NSG-209
Rochester

STATISTICAL ANALYSIS

OF

MARS MICROBE DETECTION SYSTEM III

I. Introduction

The statistical analysis of the data obtained from the "Wolf Trap" experiment will be based on the growth model given graphically in Figure 1. This model assumes that the observed response is an additive combination of soil settling, growth of first organism, growth of second organism, and a residual error. More specifically these assumptions are

1. The soil settling curve can be represented by a known function $f(\theta,t)$ with unknown parameter θ which may be vector valued. As a first approximation $f(\theta,t)$ is taken to be a negative exponential function

$$f(\theta,t) = K_o e^{-\beta_o t} \qquad t \geq 0$$

where K_o and β_o will be estimated from the data. It is tacitly assumed that the time of the start of the experiment ($t = 0$) is known.

2. The growth of the first organism is exponential beginning at time τ_1 and ending at time τ_2. Both τ_1 and τ_2 are unknown and will be estimated from the data. The duration of the experiment may not be long enough to estimate τ_2 but hopefully of sufficient duration to estimate τ_1. The

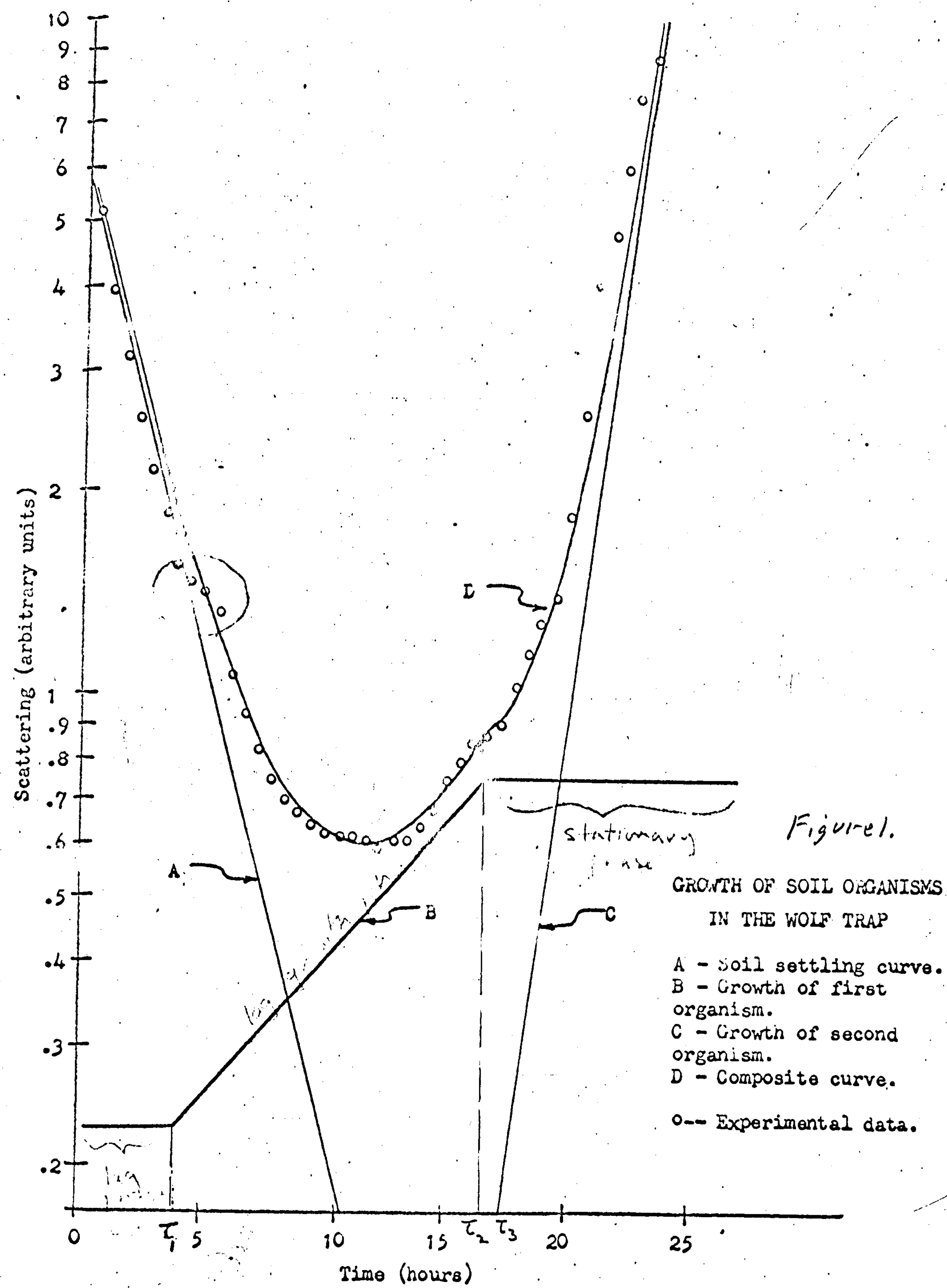
Figure 1.
GROWTH OF SOIL ORGANISMS
IN THE WOLF TRAP
A - Soil settling curve.
B - Growth of first organism.
C - Growth of second organism.
D - Composite curve.
o-- Experimental data.
Scattering (arbitrary units)
Time (hours)
10
9
8
7
6
5
4
3
2
1
.9
.8
.7
.6
.5
.4
.3
.2
0
5
10
15
20
25
τ_1
τ_2
τ_3
A
B
C
D
stationary

response due to the growth of the first organism is

$$K_1 e^{\beta_1(t-\tau_1)} \qquad \tau_1 \le t < \tau_2$$

$$K_1 e^{\beta_1(\tau_2-\tau_1)} \qquad t \ge \tau_2$$

where K_1 and β_1 are estimated from the data.

3. The growth of the second organism is also exponential beginning at time τ_3 and ending at time τ_4. Again either of these times may be greater than the duration of the experiment. Also two possible conditions can arise: $\tau_2 < \tau_3$ and $\tau_2 > \tau_3$. The response due to the growth of the second organism is

$$K_2 e^{\beta_2(t-\tau_3)} \qquad \tau_3 \le t \le \tau_4$$

$$K_2 e^{\beta_2(\tau_4-\tau_3)} \qquad t > \tau_4 \ .$$

4. The residual errors e_t are independently and normally distributed with zero mean and unknown variance σ^2. The normality assumption is partially justified by making the number of bits per word large enough so that the quantizing error is small compared to the equipment errors which are assumed to be normally distributed.

Proceeding in the above manner one could postulate any finite number of growth organisms and estimate the corresponding unknown parameters.

II. Derivation of the estimates. Based on our additive assumptions with two growth organisms and $\tau_2 < \tau_3$, the observed response y_t at time t is

$$\begin{aligned}
&\text{(a)} \quad y_t = K_o e^{-\beta_o t} + e_t && 0 \le t < \tau_1 \\
&\text{(b)} \quad\ \ = K_o e^{-\beta_o t} + K_1 e^{\beta_1(t-\tau_1)} + e_t && \tau_1 \le t < \tau_2 \\
(1)\ &\text{(c)} \quad\ \ = K_o e^{-\beta_o t} + K_1 e^{\beta_1(\tau_2-\tau_1)} + e_t && \tau_2 \le t < \tau_3 \\
&\text{(d)} \quad\ \ = K_o e^{-\beta_o t} + K_1 e^{\beta_1(\tau_2-\tau_1)} + K_2 e^{\beta_2(t-\tau_3)} + e_t && \tau_3 \le t < \tau_4 \\
&\text{(e)} \quad\ \ = K_o e^{-\beta_o t} + K_1 e^{\beta_1(\tau_2-\tau_1)} + K_2 e^{\beta_2(\tau_4-\tau_3)} + e_t && \tau_4 \le t
\end{aligned}$$

If $\tau_2 > \tau_3$, the above equations are modified as follows:

$$\begin{aligned}
&\text{(b}'\text{)} \quad y_t = K_o e^{-\beta_o t} + K_1 e^{\beta_1(t-\tau_1)} + e_t && \tau_1 \le t < \tau_3 \\
(1)\ &\text{(c}'\text{)} \quad\ \ = K_o e^{-\beta_o t} + K_1 e^{\beta_1(t-\tau_1)} + K_2 e^{\beta_2(t-\tau_3)} + e_t && \tau_3 \le t < \tau_2 \\
&\text{(d}'\text{)} \quad\ \ = K_o e^{-\beta_o t} + K_1 e^{\beta_1(\tau_2-\tau_1)} + K_2 e^{\beta_2(t-\tau_3)} + e_t && \tau_2 \le t < \tau_4
\end{aligned}$$

Based on the assumptions that the e_t are independently and normally distributed with mean zero and variance σ^2, the method of maximum likelihood (MML) will be used to estimate K_i, β_i, τ_i, $i = 0,1,2$, and σ^2. This procedure leads to a system of simultaneous transcendental equations which are solved by an iterative procedure in Appendix A.

Estimation of τ_1, K_o, K_1, β_o, β_1 and possibly τ_2.

It is further assumed that the primary interest centers about τ_1 and β_1, i.e. is there bacterial growth and at what time does it begin?

Several cases arise depending upon whether or not τ_2 occurs before the end of the experiment and before or after τ_3. To simplify the initial computations, the effect of a possible second organism will be neglected. The two models, labeled A and B, under consideration are 1(a), (b), and 1(a), (b), (c), respectively, depending on whether τ_2 occurs.

<u>Model A</u>. From an inspection of the data, choose a time t_f as the termination of the experiment. Given these f consecutive observations choose a likely value for τ_1 by a visual inspection of the data and maximize the likelihood function or its natural logarithm

$$(2)\quad L = \left(\frac{1}{2\pi\sigma^2}\right)^{f/2} e^{-1/\sigma^2 \sum_{i=1}^{n_1-1} (y_1 - K_o e^{-\beta_o t_i})^2 + \sum_{i=n_1}^{f} (y_i - K_o e^{-\beta_o t_i} - K_1 e^{-\beta_o (t_i - \tau_1)})^2}$$

$$(3)\quad \ln L = -\frac{f}{2} \ln 2\pi\sigma^2 - \frac{1}{\sigma^2} \sum_{i=1}^{n_1-1} (y_i - K_o e^{-\beta_o t_i})^2 + \sum_{i=n_1}^{f} (y_i - K_o e^{-\beta_o t_i} - K_1 e^{\beta_1 (t_i - \tau_1)})^2$$

where n_1 is the number of observations that have been taken up to and including the time estimates for τ_1. L or ln L is maximized by setting

$$\frac{\partial \ln L}{\partial K_o} = \frac{\partial \ln L}{\partial K_1} = \frac{\partial \ln L}{\partial \beta_o} = \frac{\partial \ln L}{\partial \beta_1} = 0$$

and solving the following four simultaneous transcendental equations by an iterative technique suggested in Appendix A. This method transforms the non-linear problem to a linear one by using a first order Taylor series expansion of $f(t,\theta)$.

$$\frac{\partial \ln L}{\partial K_o} = \frac{2}{\sigma^2} \sum_{i=1}^{n_1-1} e^{-\beta_o t_i}(y_i - K_o e^{-\beta_o t_i}) + \sum_{i=n_1}^{f} e^{-\beta_o t_i}(y_i - K_o e^{-\beta_o t_i} - K_1 e^{\beta_1(t_i - t_{n_1})})$$

$$\frac{\partial \ln L}{\partial \beta_o} = \frac{2}{\sigma^2} \sum_{i=1}^{n_1-1} -K_o t_i e^{-\beta_o t_i}(y_i - K_o e^{-\beta_o t_i}) + \sum_{i=n_1}^{f} -K_o t_i e^{-\beta_o t_i}(y_i - K_o e^{-\beta_o t_i} - K_1 e^{\beta_1(t_i - t_{n_1})})$$

$$\frac{\partial \ln L}{\partial K_1} = \frac{2}{\sigma^2} \sum_{i=n_1}^{f} e^{\beta_1(t_i - t_{n_1})}(y_i - K_o e^{-\beta_o t_i} - K_1 e^{\beta_1(t_i - t_{n_1})})$$

$$\frac{\partial \ln L}{\partial \beta_1} = \frac{2}{\sigma^2} \sum_{i=n_1}^{f} K_1 (t_i - t_{n_1})\, e^{\beta_1(t_i - t_{n_1})}(y_i - K_o e^{-\beta_o t_i} - K_1 e^{\beta_1(t_i - t_{n_i})})$$

Denoting the estimates of K_o, K_1, β_o, β_1 which make the above partial derivations zero by k_o, k_1, b_o, b_1 we have the following four equations.

$$\sum_{i=1}^{n_1-1} e^{-b_o t_i}(y_i - k_o e^{-b_o t_i}) + \sum_{i=n_1}^{f} e^{-b_o t_i}(y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_i - t_{n_1})}) = 0$$

$$\sum_{i=1}^{n_1-1} t_i e^{-b_o t_i}(y_i - k_o e^{-b_o t_i}) + \sum_{i=n_1}^{f} t_i e^{-b_o t_i}(y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_i - t_{n_1})}) = 0$$

(4)

$$\sum_{i=n_1}^{f} e^{b_1(t_i - t_{n_1})}(y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_i - t_{n_1})}) = 0$$

$$\sum_{i=n_1}^{f} (t_i - t_{n_1}) e^{b_1(t_i - t_{n_1})}(y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_i - t_{n_1})}) = 0$$

The procedure for finding the maximum likelihood estimate $\hat{\tau}_1$ of τ_1 is as follows:

1. Choose an initial n_1. Solve equations (4) and compute

$$Q = \sum_{i=1}^{n_1-1} {y_i - k_o e^{-b_o t_i}}^2 + \sum_{i=n_1}^{f} {y_i - k_o e^{-b_o t_i} - k_1 e^{b_o(t_i - t_{n_1})}}^2$$

2. Choose another n_1 and repeat the calculations in the preceding step.

3. Repeat the above procedure until a local minima for Q is obtained. This is equivalent to maximizing L or ln L.

4. Let m be the value of n_1 that maximizes Q. Then

$$\hat{\tau}_1 = t_m$$

<u>Point estimations of K_o, K_1, β_o, β_1, σ^2.</u> The solutions of equations (4) with $n_1 = m$ give the maximum likelihood (or least squares) estimates k_o, k_1, b_o and b_1 of the parameters K_o, K_1, β_o, β_1 respectively. The maximum likelihood estimate of σ^2 is

$$\hat{\sigma}^2 = \frac{Q_{min}}{f} .$$

<u>Confidence Intervals for β_1 and τ_1. (Model A).</u>

Using large sample theory for the distribution of maximum likelihood estimates a random interval, which contains the unknown parameter $(1-\alpha)\%$ of the time, can be constructed provided certain mild regularity conditions are satisfied. Such random intervals are called confidence intervals. For $t_f < \tau_2$ (Model A) the $(1-2\alpha)$ confidence interval for β_1 is

$$b_1 - z_{1-\alpha}\sigma(b_1) \le \beta_1 \le b_1 + z_{1-\alpha}\sigma(b_1)$$

where

$z_{1-\alpha}$ is the value of the unit normal random variable Z such that

$$P[Z \le z_{1-\alpha}] = 1 - \alpha$$

commonly used values are

$$z_{.975} = 1.96$$

$$z_{.995} = 2.58$$

$$\sigma^2(b_1) = \frac{\sigma^2}{K_1{}^2 \sum_{i=m}^{f} (t_i - \tau_1)^2 e^{2\beta_1(t_i-\tau_1)}}$$

and the unknown parameters are replaced by their maximum likelihood estimates.

The $(1-2\alpha)$ confidence interval for τ_1 is

$$(t_m - z_{1-\alpha}\sigma(t_m) \leq \tau_1 \leq t_m + z_{1-\alpha}\sigma(t_m))$$

where

$$\sigma^2(t_m) = \frac{\sigma^2}{K_1{}^2\beta_1{}^2 \sum_{i=m}^{f} e^{2\beta_1(t_i-\tau_1)}} .$$

Appendix B gives the derivation of these results.

Due to the finiteness of our sample and the replacement of the unknown parameters by their estimates, the above confidence intervals are only approximations.

Model B. $(\tau_2 < t_f)$. Let us now assume that the first organism has reached a saturation point in its growth at time τ_2 less than t_f which is less than τ_3. Equations 1(a), (b), (c) apply. The procedure given for Model A is modified as follows:

1. Choose t_m as in Case A.
2. From a visual inspection of the data choose initial estimates t_{n_1} and t_{n_2} of τ_1 and τ_2 respectively.
3. Minimize Q for this choice of n_1 and n_2.
4. Vary n_1 and n_2 until a local minimum, Q_{min} for Q is obtained.

Where

$$Q = \sum_{i=1}^{n_1-1} (y_i - k_o e^{-b_o t_i})^2 + \sum_{i=n_1}^{n_2-1} (y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_i - t_{n_1})})^2$$

$$+ \sum_{i=n_2}^{f} (y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_{n_2} - t_{n_1})})^2$$

Setting $\frac{\partial Q}{\partial k_o} = \frac{\partial Q}{\partial b_o} = \frac{\partial Q}{\partial k_1} = \frac{\partial Q}{\partial b_1} = 0$

gives the following system of equations.

$$\sum_{i=1}^{n_1-1} e^{-b_o t_i}(y_i - k_o e^{-b_o t_i})$$

$$+ \sum_{i=n_1}^{n_2-1} e^{-b_o t_i}(y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_i - t_{n_1})})$$

$$+ \sum_{i=n_2}^{f} e^{-b_o t_i}(y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_{n_2} - t_{n_1})}) = 0$$

$$\sum_{i=1}^{n_1-1} t_i e^{-b_o t_i}(y_i - k_o e^{-b_o t_i}) + \sum_{i=n_1}^{n_2-1} t_i e^{-b_o t_i}(y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_i - t_{n_1})})$$

$$+ \sum_{i=n_2}^{f} t_i e^{-b_o t_i}(y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_{n_2} - t_{n_1})}) = 0$$

$$\sum_{i=n_1}^{n_2-1} e^{b_1(t_i-t_{n_1})}(y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_i-t_{n_1})})$$

$$+ e^{b_1(t_{n_2}-t_{n_1})} \sum_{i=n_2}^{f} (y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_{n_2}-t_{n_1})}) = 0$$

$$(4') \quad \sum_{i=n_1}^{n_2-1} (t_i - t_{n_1}) e^{b_1(t_i-t_{n_1})}(y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_i-t_{n_1})})$$

$$+ (t_{n_2} - t_{n_1}) e^{b_1(t_{n_1}-t_{n_2})} \sum_{i=n_2}^{f} (y_i - k_o e^{-b_o t_i} - k_1 e^{b_1(t_{n_2}-t_{n_1})}) = 0$$

Point Estimates of K_o, K_1, β_o, β_1, τ_1, τ_2, σ^2.

Let m,n be the values of n_1 and n_2 which yield Q_{min}. Then

$$\hat{\tau}_1 = t_m$$

$$\hat{\tau}_2 = t_n$$

and the maximum likelihood estimates of K_o, K_1, β_o, β_1 are k_o, k_1, b_o, b_1 respectively in (4′) with

$$n_1 = m$$

$$n_2 = n$$

$$\hat{\sigma}^2 = \frac{Q_{min}}{f}$$

Confidence Intervals for β_1, τ_1.

The procedure is the same as in Model A with the obvious modification in the summation between n and f. If the number of observations in the time period $t_f - t_n$ is much greater than the number in the period $t_n - t_m$ is

$$f - n \gg n - m.$$

A simplification and a theoretical improvement in the confidence interval is obtained (see Appendix B). Under the above condition

$$\sigma^2(b_1) = \frac{\sigma^2}{fK_1^{\,2}(\tau_2-\tau_1)^2 e^{2\beta_1(\tau_2-\tau_1)}}$$

$$\sigma^2(t_n) = \sigma^2(t_m) = \frac{\sigma^2}{fK_1^2\,\beta_1^2\,e^{2\beta_1(\tau_2-\tau_1)}}$$

and the confidence intervals are as in Case A.

Appendix A. Iterative Solutions of Equations (4) and (4').

For normally independently distributed errors the method of maximum likelihood is identical with the method of least squares. The iterative procedure for finding the estimates of K_o, K_1, β_o, β_1 is given in detail in the paper by H. O. Hartley: "The Modified Gauss-Newton Method for the Fitting of Non-Linear Regression Functions by Least Squares," in Technometrics, Vol. 3, No. 2, May 1961, pp. 269-280.

The following manuals, which include a computer program, would also be extremely useful in finding the above estimates:
"The Solution of the General Least Squares Problem with Special Reference to High-Speed Computers" LA-2367 and LA2367 addenda. Los Alamos Scientific Laboratory of the University of California, Los Alamos, N.M., available from the

Office of Technical Services
U.S. Dept. of Commerce
Washington 25, D.C.

The method used in the above references consists in approximating the expected values of the response given in (1) by a first order Taylor series expansion. This reduces the non-linear problem to a linear one. An initial estimate is made of the unknown parameters and an iterative procedure is employed to obtain refined estimates of these unknown parameters. The two problems, the convergence of the refined estimates and their convergence to the correct value, can be resolved by using the iterative procedure for several initial values of the unknown parameters and then comparing the calculated response using the refined estimates with the observed values.

The Los Alamos iterative procedure is applied to the above problem as follows:

Given

$$y_i = f(x_i, \theta_1, \ldots, \theta_p) + e_i$$

where y_i is the ith observation of the dependent variable

x_i -- independent variable

$\theta_1, \ldots, \theta_p$ -- unknown parameters

$$\theta^o = (\theta_1^o, \ldots, \theta_p^o).$$

The first order Taylor expansion of f around $\theta^o = (\theta_1^o, \ldots, \theta_p^o)$ is

$$(5) \qquad f(x,\theta) = f(x,\theta^o) + \sum_{j=1}^{p} f_j(x,\tilde{\theta})(\theta_j - \theta_j^o)$$

where $\tilde{\theta} \in (\theta, \theta^o)$ and $f_j(x,\tilde{\theta}) = \left.\frac{\partial f}{\partial \theta_j}\right|_{\theta=\tilde{\theta}}$

In the remainder of the derivation $\tilde{\theta}$ will be taken equal to θ^o.

We will find $\hat{\theta}$ an estimate of θ^o by using (5) to minimize a sum of squares

$$Q = \sum_{i=1}^{n_1-1} (y_i - f(x_i,\theta)^2 + \sum_{i=n_1}^{f} (y_i - f(x_i,\theta))^2$$

$$= \sum_{i=1}^{f} ((y_i - f(x_i,\theta^o) - \sum_{j=1}^{p} f_j(x_i,\theta^o)(\theta_j - \theta_j^{\,o}))^2$$

$$0 = \frac{\partial Q}{\partial \theta_k} = -2 \sum_{i=1}^{f} [y_i - f(x_i,\theta^o) - \sum_{j=1}^{p} f_j(x_i,\theta^o)(\theta_j - \theta_j^{\,o})] f_k(x_i,\theta^o) \qquad k = 1,2,\dots,p$$

$$(6) \quad \sum_{i=1}^{f} f_k(x_i,\theta^o) \sum_{j=1}^{p} f_j(x_i,\theta^o)(\theta_j - \theta_j^{\,o}) = \sum_{i=1}^{f} f_k(x_i,\theta^o)(y_i - f(x_i,\theta^o) \qquad k = 1,\dots,p\ .$$

An initial value is chosen for θ^o and the system of p linear equations (6) is solved for θ giving a value θ^1. This process is repeated with θ^1 replacing θ^o yielding a new solution θ^2, etc. until $\theta^n - \theta^{n-1}$ is sufficiently small.

Applying this procedure to Model A, we have

$$\theta = (\theta_1, \theta_2, \theta_3, \theta_4) = (K_o, \beta_o, K_1, \beta_1)$$

$$x = t$$

$$f_1(t,\theta) = e^{-\beta_o t}$$

$$f_2(t,\theta) = -K_o t e^{-\beta_o t}$$

$$f_3(t,\theta) = e^{\beta_1(t-\tau_1)} \qquad \tau_1 \le t < \tau_2$$

$$= e^{\beta_1(\tau_2-\tau_1)} \qquad \tau_2 \le t < \tau_3$$

$$= 0 \qquad t < \tau_1$$

$$f_4(t,\theta) = K_1(t - \tau_1)e^{\beta_1(t-\tau_1)} \qquad \tau_1 \le t < \tau_2$$

$$= K_1(\tau_2 - \tau_1)e^{\beta_1(\tau_2-\tau_1)} \qquad \tau_2 \le t < \tau_3$$

$$= 0 \qquad t < \tau_1$$

From (1)

$$f(t,\theta) = K_o e^{-\beta_o t} \qquad 0 \le t < \tau_1$$

$$= K_o e^{-\beta_o t} + K_1 e^{\beta_1(t-\tau_1)} \qquad \tau_1 \le t < \tau_2$$

$$= K_o e^{-\beta_o t} + K_1 e^{\beta_1(\tau_2-\tau_1)} \qquad \tau_2 \le t < \tau_3$$

Substituting in (6) and assuming that Model A applies, we obtain the following four simultaneous linear equations in K_o, K_1, β_o, β_1:

$$\sum_{i=1}^{f} e^{-\beta_o^0 t_i}[e^{-\beta_o^0 t_i}(K_o - K_o^0) - K_o^0 t_i e^{-\beta_o^0 t_i}(\beta_o - \beta_o^0)]$$

$$+ \sum_{i=n_1}^{f} e^{-\beta_o^0 t_i}[e^{\beta_1^0(t_i-\tau_1)}(K_1 - K_1^0) + K_1^0(t_i - \tau_1)e^{\beta_1^0(t_i-\tau_1)}(\beta_1 - \beta_1^0)]$$

$$= \sum_{i=1}^{f} e^{-\beta_o^0 t_i}(y_i - K_o^0 e^{-\beta_o^0 t_i}) - \sum_{i=n_1}^{f} e^{-\beta_o^0 t_i}(K_1^0 e^{\beta_1^0(t_i-\tau_1)}).$$

(7)

$$\sum_{i=1}^{f} K_o^0 t_i e^{-\beta_o^0 t_i}[e^{-\beta_o^0 t_i}(K_o - K_o^0) - K_o^0 t_i e^{-\beta_o^0 t_i}(\beta_o - \beta_o^0)]$$

$$+ \sum_{i=n_1}^{f} K_o^0 t_i e^{-\beta_o^0 t_i}[e^{\beta_1^0(t_i-\tau_1)}(K_1 - K_1^0) + K_1^0(t_i - \tau_1)\, e^{\beta_1^0(t_i-\tau_1)}(\beta_1 - \beta_1^0)]$$

$$= \sum_{i=1}^{f} K_o^0 t_i e^{-\beta_o^0 t_i}(y_i - K_o e^{-\beta_o^0 t_i}) - \sum_{i=n_1}^{f} K_o^0 t_i e^{-\beta_o^0 t_i}(K_1^0 e^{\beta_1^0(t_i-\tau_1)})$$

$$\sum_{i=n_1}^{f} e^{\beta_1^0(t_i-\tau_1)}[e^{-\beta_o^0 t_i}(K_o - K_o^0) - K_o^0 t_i e^{-\beta_o^0 t_i}(\beta_o - \beta_o^0)$$

$$+ e^{\beta_1^0(t_i-\tau_1)}(K_1 - K_1^0) + K_1^0(t_i - \tau_1)e^{\beta_1^0(t_i-\tau_1)}(\beta_1 - \beta_1^0)]$$

$$= \sum_{i=n_1}^{f} e^{\beta_1^0(t_i-\tau_1)}[y_i - K_o^0 e^{-\beta_o^0 t_i} - K_1^0 e^{\beta_1^0(t_i-\tau_1)}]$$

$$\sum_{i=n_1}^{f} K_1^0(t_i - \tau_1)e^{\beta_1^0(t_i-\tau_1)}[e^{-\beta_o^0 t_i}(K_o - K_o^0) - K_o^0 t_i e^{-\beta_o^0 t_i}(\beta_o - \beta_o^0)$$

$$+ e^{\beta_1^0(t_i-\tau_1)}(K_1 - K_1^0) + K_1^0(t_i - \tau_1)e^{\beta_1^0(t_i-\tau_1)}(\beta_1 - \beta_1^0)]$$

$$= \sum_{i=n_1}^{f} K_1^0(t_i - \tau_1)e^{\beta_1^0(t_i-\tau_1)}[y_i - K_o^0 e^{-\beta_o^0 t_i} - K_1^0 e^{\beta_1^0(t_i-\tau_1)}]$$

A similar set of equations pertain to Model B with the summation from n_1 to f broken into two parts, one summation going from n_1 to $n_2 - 1$ and the other from n_2 to f.

The solutions obtained from (7) should be checked in (4).

The system of equations (7) can be written in matrix form.

Let $Y = AX$

where

$$Y = \begin{pmatrix} y_1 \\ \cdot \\ \cdot \\ \cdot \\ y_{n_1-1} \\ y_{n_1} \\ \cdot \\ \cdot \\ \cdot \\ y_f \end{pmatrix} \quad A = \begin{pmatrix} f_1(t_1,\theta^o) & f_2(t_1,\theta^o) & 0 & 0 \\ \cdot & & & \\ \cdot & & & \\ \cdot & & & \\ f_1(t_{n_1-1},\theta^o) & f_2(t_{n_1-1},\theta^o) & 0 & 0 \\ f_1(t_{n_1},\theta^o) & f_2(t_{n_1},\theta^o) & f_3(t_{n_1},\theta^o) & f_4(t_{n_1},\theta^o) \\ \cdot & & & \\ \cdot & & & \\ \cdot & & & \\ f_1(t_f,\theta^o) & f_2(t_f,\theta^o) & f_3(t_f,\theta^o) & f_4(t_f,\theta^o) \end{pmatrix}$$

$$X = \begin{pmatrix} K_o - K_o^0 \\ K_1 - K_1^0 \\ \beta_o - \beta_o^0 \\ \beta_1 - \beta_1^0 \end{pmatrix}$$

Then

$$A'AX = A'Y$$

$$X = (A'A)^{-1} A'Y$$

Appendix B. The large sample theory for Model B is well known and follows from the derivation given in Mood, Introduction to the Theory of Statistics, McGraw-Hill, 1950, pp. 208-211.

In Model A as we are no longer dealing with identically distributed random variables, the large sample theory used in Model B does not apply. Furthermore, the non-linearity of our model rules out the classical results of linear regression theory. The approximate results given come from the following derivation:

Let $$u_i = \frac{\partial \ln f(y_i,\theta)}{\partial\theta}$$

where y_i is given by (1) and θ in any one of the unknown parameters. The maximum likelihood equation

$$\frac{\partial \ln L(\hat{\theta})}{\partial\theta} = 0$$

is expanded in a Taylor Series about $\theta = \theta_o$.

$$0 = \frac{\partial \ln L(\hat{\theta})}{\partial\theta} = \frac{\partial \ln L(\theta_o)}{\partial\theta} + \frac{\partial^2 \ln L(\tilde{\theta})}{\partial\theta^2}(\hat{\theta} - \theta_o)$$

where

$$\tilde{\theta} \epsilon (\theta_o,\hat{\theta}).$$

In terms of u_i this equation becomes

(5) $$-\sum u_i(\theta_o) = (\hat{\theta} - \theta) \sum u_i'(\tilde{\theta})$$

Recalling

$$f(y_i,\theta) = \frac{1}{\sqrt{2\pi}\,\sigma} e^{-\frac{1}{2\sigma^2}(y_i - K_o e^{-\beta_o t_i} - K_1 e^{\beta_1(t_i-\tau_1)})^2}$$

with $\theta = \beta$.

$$u_i = \frac{1}{\sigma^2}(y_i - K_o e^{-\beta_o t_i} - K_1 e^{\beta_1(t_i-\tau_i)})K_1(t_i - \tau_1)e^{\beta_1(t_i-\tau_1)}$$

The u_i are independently and normally distributed with

$$E[u_i] = 0.$$

$$\text{Var}\,[u_i] = \sigma^2(u_i) = \frac{K_1^2(t_i - \tau_1)e^{2\beta_1(t_i-\tau_1)}}{\sigma^2}$$

also

$$u_i'(\beta_1) = \frac{\partial u_i}{\partial\beta_1} = \frac{-1}{\sigma^2}\,(K_1(t_i - \tau_1)\; e^{\tilde{\beta}_1(t_i-\tau_1)})^2 + (t_i - \tau_1)u_i$$

$$\sum_i u_i'(\beta_1) = -\frac{K_1^2}{\sigma^2}\sum_{i=1}^{m}((t_i - \tau_1)e^{\tilde{\beta}_1(t_i-\tau_1)})^2 + \sum_{i=1}^{m}(t_i - \tau_1)u_i$$

$$\approx -\frac{K_1^2}{\sigma^2}\sum_{i=1}^{m}(t_i - \tau_1)^2\, e^{2\beta_1(t_i-\tau_1)}$$

as

$$E[\sum_{i=1}^{m}(t_i - \tau_1)u_i] = 0$$

Substituting in (5)

$$b_1 - \beta_1 \approx \frac{-\sum u_i(\theta_o)}{-\frac{K_1^2}{\sigma^2}\sum_{i=1}^{m}(t_i - \tau_1)^2\, e^{2\tilde{\beta}_1(t_i-\tau_1)}}$$

$b_1 - \beta_1$ is approximately normally distributed with mean 0 and variance

$$\frac{\sigma^2}{K_1^2 \sum_{i=1}^{m} (t_i - \tau_1) e^{2\tilde{\beta}_1(t_i-\tau_1)}} \tag{6}$$

Note that an error is introduced in the evaluation of (6) by using b_1 instead of $\tilde{\beta}_1$.